Pathophysiology, Pharmacology and Therapeutics: Connecting the Dots in Advanced Pain Management

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Disclosures

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Objectives

- Design and implement an assessment strategy for a pain complaint based on the physiology of nociception and the pathogenesis of chronic pain.
- Determine anticipated clinical pain relief based on current understanding of the pathogenesis of pain and mechanisms of analgesic action.
- Design a rational multi-drug regimen based on current practice evidence.

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What's on YOUR Dance Card?

- Physiology/pathogenesis of pain
- Interviewing a patient about a complaint of pain
- Correlating history and physical assessment information to drive drug therapy decision making
- Pharmacodynamics of analgesics / rational polypharmacy analgesic regimens
- Cases
  - Chronic pain / fibromyalgia
  - Acute pain in a cancer patient
  - Post-operative pain management
  - Complex end of life pain management

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Physiology / Pathophysiology of Pain

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University of Maryland School of Pharmacy

What is this thing called PAIN?

- Pain that is an early-warning physiologic protective system
  - Essential to detect and minimize contact with damanging or noxious stimuli
  - Referred to as nociceptive pain
- Pain that is adaptive and protective
  - Heightened sensory sensitivity after unavoidable tissue damage
  - Assists in the healing of the injured body part by creating a situation that discourages physical contact and movement
- Pain that is not protective, but maladaptive, resulting from abnormal functioning of the nervous system
  - Pathological pain
  - A disease of the nervous system
    - Damage (neuropathic pain); dysfunctional pain

Woolf CJ. J Clin Inves 2010;120(11):3742-4

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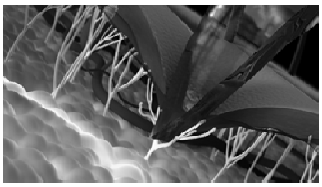
Initiation of Nociceptive Pain

- Nociceptive pain occurs as a result of the activation of the nociceptive system by noxious stimuli, inflammation or disease.

Phases of Nociceptive Pain

- Nociceptive Pain proceeds through five phases:
  - Transduction
  - Conduction
  - Transmission
  - Perception
  - Modulation



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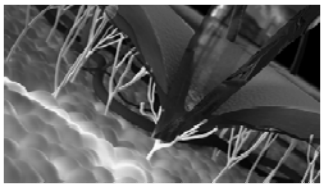
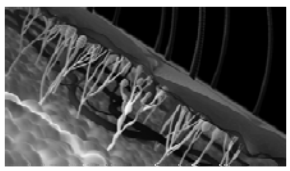


Neuropathic Pain Etiology

- Neuropathic pain involves injury or alteration of the normal sensory and modulatory nervous systems.

Neuropathic Pain Etiology

- Multiple processes are capable of producing sufficient neural alteration to produce neuropathic pain.[1]
- These processes include:
  - Abnormal nerve regeneration
  - Increased expression of membrane sodium channels
  - Disinhibition of modulatory processes
  - Decreased expression of mu-opioid receptors



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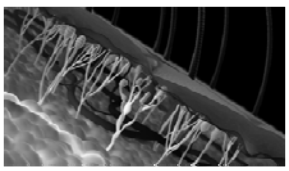

Preparing for and interviewing a patient in pain

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Southern Illinois University Edwardsville

The Initial Meeting

- Project calm, trust, and belief
  - Many patients have set unrealistic expectations regarding your meeting (good and bad)
  - We tell every patient "we believe you have pain"
- Let the patient tell YOU why they are there
  - Allow 3-5 minutes of completely open and uninterrupted discourse
  - Use open-ended questions during this time
- Avoid negative non-verbal behaviors
  - Crossed arms
  - Back to patient during charting in EMR

1. Shaw WS, et al. The effects of patient-provider communication on 3-month recovery from acute low back pain. J Am Board Fam Med 2011;24:16-25.
2. Ackerman E, et al. Motivational interviewing: A behavioral counseling intervention for the family medicine provider. Fam Med 2011;43:582-585.
3. Leila NM, et al. Training medical students to manage a chronic pain patient: Both knowledge and communication skills needed. Eur J Pain 2006;10:167-170.

Symptom Assessment or Analysis

PQRST

- Provokes
  - Palliative factors
  - Temporal factors
- Quality
  - What does it feel like
  - How to recreate
- Radiation
  - When & where (i.e. back pain)
- Severity
  - Consistent method to rate
- Timing
  - When did it start (longitudinal)
  - When is it worse / better

OLD CARTS

- Onset
- Location
- Duration
- Character
- Alleviating / Aggravating
- Radiation
- Timing
- Severity

History of Present Illness

- Separate each pain syndrome and rank disability
- Ask for perceived causative events
- Identify functionality or activities impaired
- Obtain patient goals for treatment
  - We always ask "what would you like for us to do for you"
  - During this section of interview, education is paramount
  - What activities can we work on improving?
- Query non-pharmacologic interventions
  - History, duration, and result
  - Willingness to try non-pharmacologic intervention
  - Candid discussion on barriers to non-pharm interventions
- Specifically rule out current / previous psych care

Non-Pharmacological Interventions

- Physical therapy
  - Terrestrial
  - Aquatic
- Acupuncture / auricular therapy
- Osteopathic Manipulation Therapy (OMT)
- Chiropractic
- Massage therapy
- Yoga, stretching, swimming
- Surgical consultation / history
- Interventional consultation / history
  - Injections, blocks or pumps?

1. Brantingham JW, et al. Manipulative therapy for shoulder pain and disorders: Expansion of a systematic review. J Manipulative Physiol Ther 2011;34:314-346.
2. Posadzki P, et al. Osteopathy for musculoskeletal pain patients: A systematic review of RCTs. Clin Rheumatol 2011;30:285-91.

Medication History

- Self report versus health profession administered
- Current meds, dose, duration
  - Planned or accidental drug holiday?
- Previous medications
  - Successful
  - Failed (always dig deep regarding "failed" meds)
- Over the counter meds
  - Herbals, acetaminophen, NSAIDs, topicals
- Drug allergies

1. Malat J, Kahn DA. Clinical barriers to effective pharmacotherapy in co-occurring psychiatric and substance abuse disorders. J Psychiatr Pract 2011;17:360-367.
2. Montpetit LM, et al. Evaluation of a patient-completed versus health professional-conducted medication history. Drug Intell Clin Pharm 1988;22:964-9.

Focused Review of Systems (ROS)

- Hair to toenails
- Disease, med adverse effects, function
- CNS / General
  - Sleep latency, sleep duration, snoring, hygiene, fatigue
  - Mood, manic or hypomanic s/sx, suicidical or homicidal
    - Consider depression, anxiety, PTSD, or bipolar screen
  - Visual changes, headache
- CV / Pulmonary
  - Chest pain, shortness of breath, heart palpitations (methadone)

Focused ROS (continued)

- GI / GU
  - Nausea, vomiting, diarrhea, constipation
  - Last BM, frequency of BM, consistency of BM
  - Urinary retention or incontinence
  - Sexual dysfunction
- Extremities, Neuro, Musculoskeletal
  - Itching
  - Paresthesias
  - Weakness or foot drag / drop
  - Twitching or myoclonus

Social History

- Perhaps the most important piece of interview!
- Tobacco abuse?
  - How long, how often, how soon after awakening
  - Risk factor for opioid misuse, neurosurgeons wont work
- Alcohol use?
  - How long (ago), how often, how soon, how much?
  - We need volume vs. quantity (1 beer has wide variability)
- Recreational drug use?
  - I ask about each specifically
  - "what would I find if I ordered a drug screen today?"
- Violence, abuse, or rape?
  - Choose the venue and rapport prior to proceeding but its important information

Family History

- Concentrate on associated information
- History of similar pain problems in 1st degree relatives
- History of polysubstance abuse?
  - Patients will often be more willing to provide this info
  - Insight into family dynamics, support structure, and risk
- We will ask if brothers or sisters specifically:
  - Abuse or have abused street and prescription drugs
  - Abuse or have abused alcohol
  - Were sexually or violently abused during childhood

Conclusions

- Multi-dimensional assessment tools DO NOT replace a live interview / history
- Use a consistent method
- Allow open-ended time and then focus your time
- Avoid judgmental statements, replies, or nonverbals
- All information is important!

Putting it Together: Assessment and Pathophysiology

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The University of Iowa Hospitals and Clinics

Assessing Pain

Subjective data from patient:
- Quantity / quality of pain
- Functionality
- Review of systems
- History

Objective data from:
- Physical Exam
- Laboratory tests
- Diagnostic tests, scans, etc.
- Prescription refills, PMP

+

Pathophysiology of Pain

↓

What kind of pain are we treating?
Nociceptive (somatic, visceral)
Neuropathic

↓

Design a therapeutic strategy!

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Palliating or Provoking Factors

Any Patient

- Touch
- Temperature
- Movement
- Sleep
- Co-morbidities
- Injections
- Medications

Our Patient

- Provoking
  - Lifting
  - Sitting at the computer
  - Depression
  - Vitamin D deficiency
- Palliating
  - Move around
  - Heat
  - Flaxseed pillow
  - Trigger point injections
  - Massage
  - Medications

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Medication Therapies

- Past
  - Corticosteroids (!)
  - ✓ Pregabalin (Lyrica®) (feet felt numb)
  - ✓ Milnacipran (Savella®) (relief didn't last)
- Current
  - ✓ Tramadol ER 200mg PO Q AM
  - ✓ Duloxetine (Cymbalta®) 60mg PO Q AM
  - Cyclobenzaprine (Amrix®) 15mg PO Q PM (+/-)
  - ✓ Amitriptyline 200mg PO Q HS (helped initially)
  - Vitamin D 2000 – 4000 IU PO Q DAY (+/-)
  - Hydrocodone/Acetaminophen (Vicodin®) ? about 12 tabs/wk

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Quality

Any Patient

- Neuropathic
  - Sharp, shooting, lancinating
  - Constant, burning, tingling, dysaesthetic
- Nociceptive
  - Dull, aching, throbbing, swelling, stiffness
- Visceral
  - Nausea, gnawing

Our Patient

- "Flu-like", achy
- "Run over by a bus"
- Stiff, harder to move in morning
- "Trigger points" in her back

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Radiating / Referred / Regional

Any Patient

- Localized to a specific region, extremity
- Radiating
- Referred

Our Patient

- Regional
  - Localized to shoulder blades and neck muscles
  - Hip "bursitis"
  - "Arthritis" in feet
- Radiating / Referred
  - Demonstrated via massage therapist

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Severity

Any Patient

- Uni-dimensional tools
- "Put a number on it"
  - NRS, VAS
  - Mild, moderate, severe
- "Pick a face"
  - Wong-baker
- Try to assess parameters
  - Worst, best, average, now
  - What is acceptable to pt?

Our Patient

- Today 7-8 out of 10
- Avg pain of 8 out of 10
- Best pain 4 out of 10

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Temporal / Timing

Any patient

- Onset
- Duration
- Patterns
- Chronic / intermittent
- Breakthrough pain
- Flares in chronic pain

Our patient

- Inciting event
- Maybe fall from horse
- Duration - years
- Chronic, with flares
- "Worse as the day goes on"

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YOU (associated symptoms)

Any Patient

- Other symptoms
  - Fatigue
  - Poor appetite
  - Poor sleep
  - Depression
  - Cognitive changes
  - Change in vitals

Our Patient

- Mood "depressed"
- Fatigue
- Tired
- Poor sleep
- Cognitive
  - poor memory
  - "foggy"
  - "mix up words"

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Functionality

Any Patient

- ADL's, appetite, sleep, social interactions, hobbies, work, enjoyment of life
- Multidimensional Tools
  - SF-36
  - McGill Pain Questionnaire
  - Brief Pain Inventory

Our Patient

- "Can't work out like I used to"
- Can't ride her horse
- "Any 'clear' morning is great"
- Sleep poor
- Can't take laundry up and down stairs
- Has missed work due to "fog"

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Review of Systems

Any Patient

- General / Vitals
- Cognitive
- HEENT
- Skin / nails
- CV / pulmonary
- GI / GU
- Extremities, neurologic, musculoskeletal

Our Patient

- Denies h/a, visual change
  - Dry mouth
- Memory problems, mixing up words
- Nausea/vomiting/diarrhea
  - Constipation - self treated
  - Urinary retention with difficulty emptying bladder
- Upper back and neck pain, hip pain, foot pain

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ROS Red Flags

- Cauda Equina Syndrome (Spinal Stenosis)
  - Urine or stool incontinence, saddle anesthesia, foot drop, weakness and / or radicular pain
- Opioid hypogonadism
  - Depressed mood, difficulty with sleep, sexual dysfunction, amenorrhea, alopecia
- Methadone red flags
  - Oversedation, new onset / worsening of snoring, heart palpitations
- Urinary retention
  - Difficulty initiating stream or feeling incompletely empty
- Opioid withdrawal syndrome
  - Anxiety, diaphoresis, nausea, vomiting, diarrhea, others

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History

Any Patient

- Personal medical history / co-morbidities
- Social history
  - EtOH
  - Tobacco
  - Recreational drugs
- Family history
  - Depression
  - Substance abuse

Our Patient

- Depression
- Vitamin D deficiency?
- Occasional EtOH intake
- Non-significant family history

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What does it look like?

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Physical Exam

- HEENT
  - Constricted pupils, dry mouth
- Chest/CV/Pulmonary
  - Arrhythmia, turbulent air movement, rales
- Abdomen
  - Liver enlargement, bowel sounds, hernia
- Extremities
  - Skin / nail color, hair pattern/loss, temperature, edema
- Neurologic
  - Motor weakness, hyperalgesia, allodynia, anesthesia
- Musculoskeletal
  - Trigger points, tender points, inflamed joints, myalgias, arthralgias

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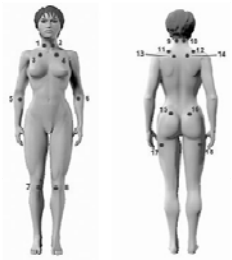

Classic Fibromyalgia Tender Points

www. fibromyalgialife.net

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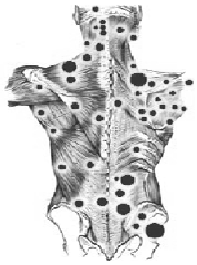

Classic Myofascial Trigger Point Locations

www.physiotherapy-health.blogspot.com

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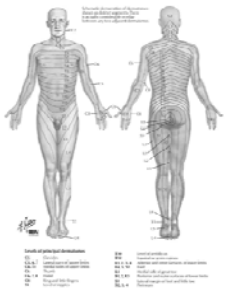
Radicular Pain

- Where would we expect to see
  - C5-6 disc herniation
  - L4-5 disc herniation
  - T8 distribution



www.backpain-guide.com

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Labs / Interpretation

- Labs commonly ordered for evaluation
  - Acute phase reactants (ESR, CRP, anti-CCP, ANA, RF)
  - Thyroid stimulation hormone (TSH)
  - 25-OHD (vitamin D)
  - IgM & IgG Lyme titer
  - Vitamin B12 and rapid plasma reagin (neurosyphyllis)
  - Various viral panels / screens
- Labs to monitor medications
  - Electrolytes
  - Renal, liver function
  - Urine toxicology screens
  - Bone density
  - Gonadotropin levels

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Diagnostics / Interpretation

- Electromyography and nerve conduction velocity testing
  - Anesthesia, paresthesias, motor weakness
- Plain film radiography, MRI, and CT (w/wo contrast)
  - Bones, nerves, joints, and internal organs
- Bone scans
- Sleep study / polysomnography
- Functional capacity examination
- Diagnostic nerve blocks and discography

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CT/MRI

- Arthrosis, spondylosis, arthropathy – osteoarthritic changes
- Spondylolisthesis – vertebral slip from position
- Spondylolysis – defect / fracture of vertebral body
- Spondylitis – inflammation of joint b/w vertebrae
- Nerve root impingement – impinged nerve root
- Neuroforaminal stenosis – space around spinal cord is smaller than normal
- Thecal sac encroachment – something pushing on spinal cord
- Disc dessication – dehydrated and flattened disc
- Herniation or protrusion – movement outside margins
- Annular rent or tear – destruction of the nucleus pulposis of the disc

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Does the rubber meet the road?

- Does clinical presentation = objective evaluation?
  - Radicular low back pain in L5 distribution
    - Does this match MRI findings (herniated disk at L4-5)?
  - Stocking – glove paresthesias / anesthesia
    - History of alcohol use?
    - Uncontrolled diabetes mellitus?
  - Headache
    - Is there cervical spine disease?
    - Are there upper back, neck or head trigger points?

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Pharmacodynamics of Analgesics: Rational Polypharmacy Analgesic Regimens

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University of Maryland School of Pharmacy

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Pharmacotherapeutic Options

- Non-opioids
  - Acetaminophen
  - NSAIDs
    - Systemic, Topical
- Opioids
  - Morphine, oxycodone
  - Hydrocodone, hydromorphone
  - Methadone, fentanyl
  - Tramadol, tapentadol
  - Codeine, meperidine
  - Buprenoprhine
- Co-analgesics (adjuvant agents)
  - Tricyclic antidepressants
  - SNRIs, SSRIs (?)
  - Gabapentin/pregabalin
  - Other anticonvulsants
  - Anti-arrhythmics
  - Capsaicin
  - Ketamine
  - Skeletal muscle relaxants

Acetaminophen

- MOA – COX-1/COX-2 inhibitor with minimal peripheral effects, primarily central effects
- Analgesic (mild to moderate pain) and antipyretic
  - NOT neuropathic pain
- Weak anti inflammatory effects
  - Poor ability to inhibit COX in the presence of high concentrations of peroxides (found at sites of inflammation)
- Adverse effects / patient-related variables
  - Hepatotoxicity with overdose
    - Malnourishment, recent fasting
    - Alcoholism, regular and heavy use of alcohol
    - Pre-existing liver disease
    - Concomitant use of other potentially hepatotoxic drugs
  - Renal effects, cardiovascular effects, hematologic effects

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NSAIDs

- MOA – COX-1/COX-2 inhibitors both in the periphery and centrally
  - COX-1 (constitutive) – GI protection, platelet function
  - COX-2 (induced) – pain, inflammation
- Analgesic (mild to moderate pain; adjunctively for severe pain), anti-inflammatory and antipyretic
  - NOT neuropathic pain
- Available as topical or systemic therapy
- Adverse effects / patient-related variables
  - Gastric effects
    - Acute local irritation, systemic GI adverse effects
  - Cardiovascular, renal and cognitive effects

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Opioids

- MOA – Bind to opioid receptors (mu, kappa, delta)
  - Opioid receptors present periacqueductal gray and dorsal horn of the spinal cord, brainstem, thalamus, cortex
  - Opioid receptors are present where primary afferent neurons terminate in the dorsal horn of the spinal cord
    - Reduce influx of calcium at the cellular level
    - Block the release of presynaptic neurotransmitters (esp. substance P)
    - Increase potassium influx (↓ synaptic transmission)
  - Opioids reduce pain transmission by activating inhibitor pathways that originate segmentally in the spinal cord, and supraspinally
    - GABA pathway is a major inhibitor neurotransmitter system; opioid can activate the GABA system, which inhibits pain transmission
  - Opioid receptor presence in midbrain PAG, nucleus raphe magnus, and rostral ventral medulla help inhibit pain via descending inhibitory pathway
  - Opioid receptors have been found in the periphery as well
  - Methadone weakly inhibits NMDA receptor

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Opioids (continued)

- Tramadol and tapentadol have additional MOA
  - Inhibits reuptake of NE (both) and 5HT (tramadol)
- Analgesic (moderate to severe pain)
- Adverse effects / patient-related variables
  - Constipation, post-operative ileus
  - Nausea and vomiting / post-operative nausea and vomiting
  - Hypotension
  - Urinary retention
  - Myoclonus
  - Mental status changes
  - Sedation or cognitive impairment
  - Respiratory depression
  - Biliary spasm
  - Pruritus

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Tricyclic Antidepressants

- MOA – Increase activity in endogenous monoaminergic pain modulating pathways
  - Specific pathways originate from neuronal pools in the brainstem and descend to the spinal cord, where they release substances that inhibit the transmission of nociceptive impulses
    - Serotonin (5HT), Norepinephrine (NE)
  - By blocking reuptake of 5HT and NE at the synapse, TCAs increase activity in these pathways
    - NE > 5HT in the endogenous analgesia pathways
    - 5HT has a significant role in treating depression (prevalent in chronic pain)
  - TCAs also block peripheral sodium channels
  - Analgesic effect is separate from antidepressant effect
- Multipurpose adjuvant analgesic / neuropathic pain
- Adverse effects – antimuscarinic, sedation, orthostasis, cardiotoxicity, sexual dysfunction, drug interactions

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Other Antidepressants / Adjuvants

- SNRIs – duloxetine, milnacipran, venlafaxine, bupropion
- Tetracyclic compound – mirtazapine
- SSRIs (??) – fluoxetine, paroxetine, sertraline

- Corticosteroids (cancer population)
- Alpha-adrenergic agonists (clonidine, tizanidine)
- Cannabinoids

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Gabapentinoids (Gabapentin/Pregabalin)

- MOA – Blockade of presynaptic voltage-gated ion channels
  - Prevents generation of spontaneous ectopic discharges
  - Bind to presynaptic voltage-gated calcium channels and inhibit calcium influx and the release of excitatory neurotransmitters from primary afferent nerve fibers
  - May enhance overall GABA-mediated inhibitory tone
- Persistent neuropathic pain
- Adverse effects / patient-related variables
  - Dizziness, sedation, ataxia
  - Confusion, weight gain
- Other anticonvulsants: carbamazepine, clonazepam, divalproex sodium and valproic acid, phenytoin, oxycarbazepine, topiramate, lamotrigine, lacosamide

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Other Analgesics

- Capsaicin
- Sodium channel blockers
  - Lidocaine (i.v., topical)
  - Mexiletine, flecainide
- Gamma aminobutyric acid (GABA) agonists
  - Baclofen
- N-methyl-D-aspartate receptor antagonists
  - Ketamine
  - Other (dextromethorphan, memantine, amantadine)
- Ziconotide
  - Nonopioid intrathecal analgesic
  - Acts by blocking N-type calcium channels in the dorsal horn of the spinal cord

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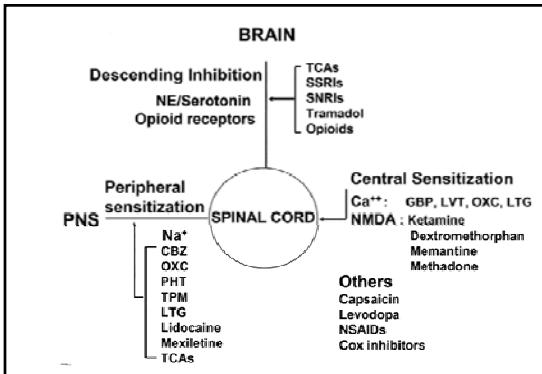

Fig. 4. Mechanistic stratification of antineuralgic agents. PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPA = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressant; NE = norepinephrine; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; GBP = gabapentin; LVT = levetiracetam; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal antiinflammatory drug.

Beydoun A, Backonja M. J Pain Sx Manage 2003;25:S18-S30

Case 1

- Patient is a 44 year old woman with a history of fibromyalgia.
- Current medications include:
  - Tramadol ER 200 mg po qam
  - Duloxetine 60 mg po qam
  - Cyclobenzaprine 15 mg ER qpm
  - Amitriptyline 100 mg, 2 tabs qhs
  - Alprazolam 0.25 mg po qhs prn
  - Cholecalciferol 400 IU 1 tab qd
  - Hydrocodone/acetaminophen 5/500 mg prn
  - Cetirizine 5 mg po qam prn
- She is not content with her current level of pain control

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Case 2

- Patient is a 53 year old woman with a history of stage IIIa ovarian cancer.
- Patient reports to Emergency Room reporting low back / left hip pain that she rates as 10/10
- Her current analgesics include:
  - Meloxicam 15 mg po qam
  - Acetaminophen 500 mg po q8h prn
- What's the scoop?

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Case 3

- Patient is a 67 year old man who presents to pre-op clinic prior for a scheduled right TKA.
- History of peripheral sensory neuropathy in both feet related to his diabetes.
- Current analgesics include:
  - Morphine ER 30mg bid
  - Oxycodone/acetaminophen 5/325 mg 2 tabs q6h prn (8/day)
  - Ibuprofen 600 mg qid
  - Amitriptyline 25 mg qhs
- What's the plan for pain management?
  - Pre-emptive analgesia
  - Handling opioid tolerance
  - Increased monitoring

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Case 4

- JB – 55 year old woman with end-stage lung cancer admitted to hospice, now in inpatient unit receiving i.v. PCA hydromorphone 80 mg/hour with 40 mg bolus
- Patient continues to complain of pain
- Patient also complains of muscle twitching and jerking
- Patient is requesting assisted suicide, or at least palliative sedation
- What's a pharmacist to do?

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